St. Jude Faculty Mentors and Projects for the 2017-2018 Summer Plus Fellowship

Jinghui Zhang, PhD
Chair
Department: Computational Biology

Research in the Zhang Lab focuses on understanding the genetic and epigenetic landscape of pediatric cancer through the development of novel approaches that integrate whole-genome sequencing data with RNA sequencing, copy number variation, structural variation, telomere content and gene expression data. This work combines large-scale genomic data with the development or application of computational algorithms and visualization tools to provide high-quality analysis to gain novel biological insight in the genetic or epigenetic changes in the cancer genome. Using this approach, we have characterized the genomic landscape of over 2000 pediatric cancers. These have included 700 pediatric tumors and matched non-tumor germline samples as part of the St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project (PCGP). This rich data set enables us to explore additional genetic architecture that can be used for other genetic research initiatives. Specifically, we are interested in exploring the possibility of determining the phase of haplotypes based on the allelic imbalance patterns observed in the tumor genome. This information will be highly useful for determining linkage disequilibrium important for genetic studies for complex diseases including cancer. Furthermore, the information can be used to evaluate compound heterozygosity for closely linked loci to determine the genetic inheritance pattern.

The Rhodes Summer Plus student will participate in the above mentioned research. In particular, a student with solid training in computer science and a general knowledge about genetics will develop new approaches to identify haplotypes from tumor genomes by analyzing the allelic imbalance signature of a paired germline sample. A qualified student shall be able to use the computer cluster and the Linux environment (or with minimum training), has strong motivation for research, has a demonstrated track record for solving problem through hard work with minimum supervision, capable of exploring new analytical approach, and has scientific curiosity or training (preferred) in genetics.

Xiang Chen, PhD
Assistant Member
Department: Computational Biology

Research in Dr. Chen’s lab focuses on integrating computational and experimental approaches to understand combinatory roles of genetic alterations and epigenetic deregulations, tumor microenvironment and their functional impacts in pediatric solid tumors. Specifically, we are interested in exploring the molecular mechanisms leading to tumor relapse in pediatric rhabdomyosarcoma (RMS). RMS is the most common pediatric soft tissue tumor with an overall survival rate of 64%, lower than many other pediatric cancers. Despite initial complete or near complete response to systematic therapy, 30% of patients will eventually relapse. There is no effective salvage therapy at relapse and survival after relapse is poor (17–32%), underscoring the importance of elucidating the tumors' molecular mechanisms to escape front-line therapies. Our recent researches showed that 1) relapsed tumors arise from

minor subclones that survived chemotherapy and radiation; and 2) sequential relapse tumors may arise independently from different ancestors and harbor dramatically different mutation profiles. Based on these observations, we hypothesize that relapsed RMS is driven by a small subpopulation of quiescent cells that resist antitumor therapies through microenvironment dependent mechanisms. We will monitor tumor growth in patient derived xenograft (PDX) RMS models to identify recurrent mutations and deregulated pathways in RMS resistant subpopulations. In addition, we will elucidate roles of tumor-stroma interactions in promoting drug resistance and relapse in RMS. PDX models provide a unique opportunity to separate tumor cells from stromal cells based on origin. We will use single cell RNA-seq to identify 1) differential drug sensitivities among tumor subclones; 2) enrichment of tumor/stromal subclones in resistance subpopulation and 3) specific microenvironment signatures associated with therapy resistance. Overall, we will elucidate the molecular and cellular mechanism of RMS recurrence after the front-line therapy, which should facilitate the development of innovative approaches for RMS therapy. Moreover, the methods and findings developed by the proposed studies should be applicable to other pediatric solid tumors.

The Rhodes Summer Plus student will participate in the above mentioned research. In particular, a student with solid training in biological sciences and/or computer sciences will have the opportunity to work on the project at various stages depending on the student's interest and skill sets, from sample preparation and collection to analysis of sequencing data. A qualified student shall have strong motivation in research, have scientific interests in cancer research, and be able to solve problem through hard work with minimum supervision.

Charles Gawad MD, PhD
Assistant Member
Department: Computational Biology and Oncology

Cancers are initiated by and evolve through complex interactions between the genomes of single cells and their environments. Most studies to date have defined tumor biology by simultaneously analyzing DNA isolated from thousands of tumor cells. However, that approach does not determine the co-occurrence of mutations within individual cells or detect lower frequency leukemic clones. In the Gawad lab, we work to deeply understand the biology of a malignancy as a whole by first accurately characterizing the genomes of the individual cellular building blocks. We then determine the relationships between those cells to trace back the sequence of genetic events that resulted in the formation of that leukemia, as well as to estimate the probability that some of the leukemia cells will become or are already resistant to treatment. Our lab also continues to develop and employ novel biotechnological and computational single-cell sequencing tools. Our ultimate aim is to use these new data to improve our understanding of how pediatric leukemias develop, as well as to identify unique biological features of the populations of cells that do not respond to treatment.

The Rhodes Summer Plus student will work on further developing and applying these novel experimental and computational techniques to help us better understand how drug resistance develops in children undergoing treatment for leukemia. In particular, a student with training in genetics and a general knowledge of computer science will track mutations in purified cellular populations, single leukemia cells, and cell-free DNA as patients go through treatment. A qualified student has limitless curiosity that drives their passion for basic research, a demonstrated track record of solving problem through hard work with minimum supervision, and is capable of deeply understanding new scientific methods.

Mark Hatley, MD, PhD
Assistant Member
Department: Oncology

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. Despite three decades of rigorous and intensive clinical trials the overall survival of RMS has not increased from 70%. There are two histologic types of RMS, embryonal and alveolar. Embryonal RMS make up the largest proportion of RMS patients (60% of all RMS). Mutations in all three RAS genes – *NRAS*, *KRAS*, and *HRAS* – have been found in large genomic analyses of ERMS patients. These mutations are not seen in alveolar patients. These RAS mutations also coincide in patients who have a less favorable prognosis.

RAS mutations are the most common oncogenic mutation in human cancer with upwards of 30% all human tumors harboring mutations in *NRAS*, *KRAS*, and *HRAS*. They are activating mutations which cause RAS to remain "on" in a catalytically active state. This active state causes downstream pathway activation, most notably through either the MAPK, PI3K, and/or RAL-DGS pathways. However, increasing evidence indicates that not all RAS mutations are created equally. Data from several groups show different codon mutations or different intra-codon amino acid substitutions within the RAS protein have specific downstream signaling outputs that lead to different phenotypic outcomes on tumor biology and possibly therapeutic sensitivities. We hypothesize that not all of the eighteen different RAS mutations found in embryonal RMS do not have the same downstream signaling outputs and that can be correlated back to different skeletal muscle and tumor biology. The lab has developed assays to test the effect of these different mutations on skeletal myoblast differentiation into myotubes. Undifferentiated skeletal muscle is a histological and functional hallmark of RMS. Our differentiation assays serve as a screen to first predict what mutations may be the more oncogenic in RMS cells. The student(s) will perform follow-up experiments to further test the role of these mutations in both skeletal myoblasts and in the pathogenesis of RMS. The student(s) will gain exposure to a broad array of techniques including tissue culture, molecular cloning, viral expression systems, gene editing, genetically engineered mouse models, xenograft models, protein and RNA isolation, immunoblotting, real-time PCR, apoptosis assays, and possibly others as experimental results warrant. No technical prerequisites required just a willingness to learn. The students will participate and present in weekly lab journal club and lab meeting. The lab has had here outstanding students from the Rhodes Summer Plus Program that have all been very successful. One student has been a co-author on a publication and the others are likely to be soon. The laboratory has three experienced postdoctoral fellows and a seasoned lab manager/technician that will facilitate a nurturing and educational environment.

Chia-ho Hua, PhD
Associate Member
Department: Radiation Oncology

Proton therapy is one of the cutting edge research areas in the field of radiation oncology. One major challenge facing proton therapy is to predict exactly where protons stop in patients (i.e. proton range). Conventional solution is to add additional safety margins to account for this 3-3.5% uncertainty, which unfortunately irradiates the surrounding normal tissues. A very promising solution is to utilize tissue properties (electron density, atomic number) measured by spectral CT to significantly reduce the uncertainty to 1%. St. Jude Children's Research Hospital has the world's first proton therapy center with pencil beam

scanning technology designated solely for the treatment of pediatric cancer. The Department of Radiation Oncology also houses the start-of-the-art detector-based spectral CT, which was recently installed in 2016. None of the proton therapy centers in the world has both systems. We are well poised to make significant clinical impacts.

The Rhodes Summer Plus Student will participate in the research project of applying spectral CT to proton therapy. He/She will learn hypothesis-driven research design, medical imaging experiments and data processing, cutting edge CT scanners, radiation therapy techniques including proton therapy, and scientific report writing. There will be opportunities in observation of radiation therapy process and hands-on learning medical imaging equipment in the Department of Radiation Oncology. We frequently interact with radiation oncologists, medical imaging scientists, neuroradiologists, nuclear medicine physicians, biostatisticians, imaging technologists and radiation therapists. The research project is particularly suitable for students interested in pursuing careers in medical imaging, medical physics, radiation oncology, radiology, and computer science. Familiarity with medical imaging is not required but some experience in data analysis and/or computer language programming is desirable.

Mondira Kundu, MD, PhD
Assistant Member
Department: Pathology

My lab seeks to understand the molecular mechanisms underlying various disease processes, including degenerative diseases and cancer. One very exciting project in the lab stems from the observation that mice lacking specific kinases develop muscle degeneration, similar to patients with inclusion body myopathy. Students who join my lab will have the opportunity to become involved in a wide variety of activities, including performing assessments of muscle strength on mice, performing histological and immunohistochemical analyses of mouse muscle, and performing molecular analyses to examine RNA and protein expression of relevant genes. Depending on the skill level and motivation of the students, there is also the opportunity to participate in cell based assays to dissect the mechanism by which the kinases regulate muscle function.

Jamy C Peng, PhD
Assistant Member
Department: Developmental Neurobiology

My lab investigates epigenetic mechanisms that regulate stem cell functions, with a specific focus on epigenetic factors Polycomb Group proteins. Stem cells are responsible for originating and maintaining most adult tissues in the human body. Over proliferation of stem cells can cause cancer, and under proliferation of stem cells leads to a variety of diseases such as tissue dystrophy, immuno-deficiency, and even death. Therefore, understanding stem cell regulation would contribute to the understanding of human health and disease. Epigenetic factors are chromatin-associated proteins or RNAs that regulate the transmission of cellular information through mitotic divisions without changing genomic DNA sequences. The Polycomb Group proteins associate with long non-coding RNAs and critically affect development of various organ and tissue systems. We employ a multidisciplinary

approach to determine how Polycomb Group proteins and their associated factors affect stem cells and how their dysfunction contributes to human diseases.

The student will utilize mouse and tissue culture cells as the model systems to characterize how epigenetic factors influence the maintenance and/or differentiation of stem cells. The student will join a highly enthusiastic and collaborative team and learn mouse genetics as well as biochemical and cell biological techniques that include DNA and RNA purification, polymerase chain reaction, protein extract preparation, and immunofluorescence microscopy. The student will use these techniques to complete scientific projects, learn critical scientific thinking, and eventually plan and carry out their own projects.

Fabio Demontis, PhD
Assistant Member
Department: Developmental Neurobiology

The loss of skeletal muscle mass and function caused by aging (known as sarcopenia) is a debilitating frailty that decreases lifespan and quality of life in humans. Defects in proteinhomeostasis have been implicated in the loss of both muscle mass and strength during aging. Specifically, a bulk increase in protein degradation leads to decreased muscle cell size and muscle mass loss whereas insufficient degradation of misfolded proteins contributes to decreased muscle function. However the molecular mechanisms involved are largely unknown.

The ubiquitin-proteasome system is a major pathway for protein degradation in muscles and relies on the action of >600 ubiquitin ligases, which are responsible for determining the specificity of protein target degradation by the proteasome. However, despite evidence for their dysregulation in aging, the ubiquitin ligases responsible for sarcopenia are unknown. We have screened for and identified several ubiquitin ligases responsible for the loss of muscle mass and strength during aging are we are now studying them with molecular, genetics, microscopy, and proteomics approaches in the fruit fly Drosophila and in mice.

These studies promise to dissect fundamental mechanisms responsible for sarcopenia, and thus highlight possible therapeutic targets to promote human health span by inhibiting sarcopenia.

Linda Hendershot, PhD
Assistant Member
Department: Tumor Cell Biology

<u>Molecular determination of protein folding and quality control of nascent secretory pathway proteins within the endoplasmic reticulum</u>

One third of the eukaryotic proteome encodes proteins that function at the cell surface or are secreted. They are first synthesized in the endoplasmic reticulum (ER), which provides a unique chemical environment for the folding and maturation of these proteins. The ER contains distinct chaperones that assist in protein folding and quality control factors, which identify proteins that fail to mature properly and target them for degradation. A disruption in normal

protein folding or “misfolding” is a hallmark of many disease states (*e.g.,* ranging from cystic fibrosis to Alzheimer’s disease) and can result in the formation of toxic protein aggregates and widespread disruption of the cellular proteome.

Our lab is focused on understanding the biochemical and molecular properties of the chaperones and quality control machinery of the ER. BiP, a key ER chaperone, has several functional roles within the ER; it aids in protein folding, prevents aggregation of unfolded proteins, preserves the permeability barrier of the translocon through which nascent proteins enter the ER, and identifies misfolded proteins to be targeted for degradation. BiP has multiple co-chaperone proteins involved in regulating these activities, several of which belong to the ERdj family. We are currently researching how different ERdj family members direct BiP activity in these diverse and even opposing functional roles.

We are using a state-of-the-art molecular, biochemical, and cellular methods to address these areas. This includes generating recombinant DNA vectors that allow regulated knockdown of specific ERdj family members in stable cell lines. These will be used to assess ER protein folding in novel cellular systems we have developed that are coupled with *in* vitro translation and pulse-chase methods. Together these allow unique opportunities to manipulate and monitor effects on ER protein maturation. While under the supervision of Dr. Hendershot, the student will benefit from direct interactions with a post-doctoral fellow, who is intricately involved in the project. The student who works on this project will gain training in key laboratory research methods using DNA, protein and cellular techniques of the lab. In addition they will develop skills in project planning and data analysis and have the opportunity to contribute to an exciting research area at the forefront of cell biology.

<u>Identifying the mechanisms regulating the disposal of misfolded ER luminal proteins</u>

After they are translated, nascent proteins in the cell must achieve and retain a specific three-dimensional conformation in order to function properly. This process is referred to as “protein folding” and failures in this process are the cause of many diseases such as cystic fibrosis, amyloidosis, lysosomal storage diseases and Alzheimer's disease to name a few. In addition, more global problems with protein folding are observed in certain types of cancer and some viral infections, where the presence of unfolded proteins contributes to disease pathology. One third of the human genome encodes proteins that are synthesized in the endoplasmic reticulum (ER), and only correctly folded proteins that pass a type of “quality control inspection” are allowed to continue to the cell surface or extracellular space where they must function. Those proteins that fail to mature properly must be identified, extracted from the ER, and destroyed by the proteasome to ensure that they do not lead to the formation of toxic protein aggregates, in a process referred to as ER associated degradation (ERAD). Our lab is interested in understanding how the cell discriminates between nascent unfolded proteins that can eventually fold and proteins that are unable to fold and must be identified and destroyed.

The scope of this project is to widen our understanding of the molecular basis of how this triage decision is made for each ER protein and to identify the components of this critical degradation system. This information is necessary to expanding our ability to explain the pathology behind protein folding diseases in which these mechanisms are disrupted. We have developed a novel biotin-based reporter system to track misfolded ER proteins, as well as a number of dominant negative mutants and siRNA constructs that can be used to inhibit or suppress putative ERAD components. This combination of reagents and assays will allow us to determine at which step in the ERAD process each component works, which is critical information for designing

strategies for treating the growing number of diseases classified as “protein folding diseases”. To this end, the student will be involved in using our reporter assay in a cell culture system and examining the fate of misfolded proteins in the different conditions of ERAD impairment. Our lab offers a strong team-based environment and uses state-of-the-art technologies for conducting basic molecular biology, biochemistry and cell biology research. The student who will participate in this project will advance his/her knowledge in the field of protein folding and will gain valuable hands-on experience in common laboratory practices and techniques such as cell culture, molecular cloning and protein analyses (protein electrophoresis and protein-protein interactions). In addition they will develop skills in project planning and data analysis and have the opportunity to contribute to an exciting research area at the forefront of cell biology.

Fatima Rivas, PD
Assistant Member
Department: Chemical Biology & Therapeutics

Research in the Rivas Laboratory focuses on the chemical biology of natural products with an emphasis on the development of catalytic asymmetric methods to construct complex molecular architectures with promising biological properties. We are interested in identifying the next generation of therapeutic agents to treat high risk and glucocorticoid resistant acute lymphoblastic leukemia (ALL).

Current areas of research in the Rivas laboratory include syntheses of monoterpenes and sesquiterpenoids natural products. Our research integrates the scientific areas of chemical synthesis, biochemistry and molecular biology.

Learning objectives:

- Learn to design and carry out synthesis of novel chemical entities
- Learn how to handle highly sensitive, hygroscopic, and air sensitive reagents
- Learn to purify reaction mixtures using HPLC, Isolera purification systems in combination with standard methods (column chromatography, ion exchange chromatography)
- Conduct biochemical and cellular assays to evaluate compounds
- Learn how to use ChemDraw Ultra, SciFinder, ISIS Draw, and Excel for chemists
- Ability to conduct and/or interpret 1D NMR, 2D NMR, IR/UV, and Mass Spectroscopic Data
- Learn to critique, present, and write scientific articles
- Learn to work in a collaborative multi-disciplinary environment

Expected outcome:
The student will understand the process of drug discovery from compound lead to compound optimization, and be able to conduct independent and original research work. He/she will have the opportunity to present their work at either local or national meetings and publish their results in peer reviewed journals.

Jason Rosch, PhD
Assistant Member
Department: Infectious Diseases

Pneumonia is the leading cause of childhood mortality worldwide, killing over one and a half million children younger than 5 years of age each year, more so than any other infectious disease including malaria and AIDS. In the United States, pneumonia accounts for over one million hospitalizations and over fifty thousand deaths each year despite availability of antibiotics and administration of vaccines. One of the leading causes of pneumonia is the human pathogen, *Streptococcus pneumoniae*, which is the causative agent in over 6 million infections each year in the United States. Crucial to this process are a number of virulence factors, both proteins and small regulatory RNAs that mediate various facets of how the bacteria interacts with the host to cause disease. The major goals of this project are to understand the evolution of antibiotic resistance and mechanisms of gene regulation in *S. pneumoniae* with a focus on understanding how such factors impact bacterial virulence.

To gain a greater understanding of pneumococcal pathogenesis, we employ a number of techniques. Major techniques that will be utilized throughout this project include PCR, molecular cloning, protein purification, generating bacterial knockouts, transposon mutagenesis screening, Western Blotting, BSL2 culturing techniques, modeling of bacterial pneumonia in mouse models of infection, DNA and RNA isolation, and protein purification. These techniques will be used to generate knockout mutations in the pneumococcus and we will assay the cellular function and the potential role of these deletions during both bacterial colonization and invasive disease. Specific projects will focus on novel class of virulence factors identified through transposon mutagenesis. This project will provide experience in both molecular biology and genetics but also has a strong microbiology component, specifically working with bacterial pathogens.

Jun Yang, PhD
Assistant Member
Department: Pharmaceutical Sciences

Many cancer drivers are transcription factors such as MYC, nuclear hormonal receptors (estrogen receptor alpha in breast cancer and androgen receptor in prostate cancer), and translocation fusion proteins (PAX3-FOXO1, AML1/ETO, PML-RARA, EWS-FLI1) in pediatric cancers. The hormone therapy that directly targets ERa and AR has benefited tens of millions of breast and prostate cancer patients. Unfortunately, most of the other oncogenic transcription factors are difficult to directly target due to lack of specific active sites for small molecules. In addition, resistance will eventually develop in hormone therapy. Therefore, most of these patients heavily rely on intensive modalities of chemotherapy and/or radiotherapy that may cause great adverse side effects including secondary cancer. Therefore, there is an urgent need to develop novel strategies including targeting oncogenic transcription factors for cancer treatment.

Transcription factors usually complex with multiple proteins, many of which are involved in chromatin modification or remodeling. Characterization of the biological functions of these chromatin modifiers that facilitate oncogenic transcription factors may not only help us understand the epigenetic role in tumorigenesis and cancer progression but also offer a great opportunity to identify novel therapeutic targets since most of them such as histone demethylases are targetable enzymes. Currently, we are using a variety of molecular, cellular,

genetic and pharmacologic approaches and in vivo mouse models to dissect the functions of histone demethylases and other histone modifiers in pediatric cancers. We are also collaborating with Department of Chemical Biology and Therapeutics to screen histone demethylase inhibitors for cancer treatment. We will further develop novel combination therapies to target the cancer network to eradicate resistant cancer cell clones to standard therapies.

Xinwei Cao, PhD
Assistant Member
Department: Developmental Neurobiology

Our brain is the most complex organ in our body. It controls our bodily functions and interprets the world around us through our senses. It defines us as human beings through our memories and our ability to plan for the future. Fundamental to brain development are neural stem/progenitor cells, which give rise to neurons and glia, the building blocks of a mature brain. Our lab seeks to understand how neural stem/progenitor cells are regulated so they can give rise to the right number and type of neurons and glia. Understanding this question will help us decipher the cause of some neural developmental disorders (such as microcephaly: small brain), the cause of certain brain tumors, and the genetic changes leading to brain size increase during evolution.

We mainly use the mouse brain as a model to tackle our questions because many fundamental mechanisms controlling human brain development are conserved in the mouse brain. We have generated mouse mutants with various brain development defects. We use molecular biology, cell biology, histology, and biochemistry approaches to understand how a gene, protein, or signaling pathway affects the cellular behaviors of neural stem/progenitor cells and how the behaviors of neural stem/progenitor cells influence the overall structure and composition of the brain.

We welcome students with deep interest and curiosity in biology to work in our lab. The student should have basic knowledge in general biology, molecular biology, cell biology, biochemistry, and genetics. We expect the student to be self-motivated, proactive, intelligent, and hard-working. As learning is the whole purpose of this program, the student should be willing to learn and should take criticism well.

Jian Zuo, PhD
Member
Department: Developmental Neurobiology

Please see the description of two projects in my lab for 2017 Rhodes Summer Plus Program. The student candidates can choose either of them.

Project 1: Auditory hair cell regeneration

Hearing loss is the third most common health impairment and the most common occupational illness in the United States. Approximately 90% of this hearing loss is due to damage or loss of the auditory mechanosensory cells, hair cells. Many things contribute to loss of hearing

including aging, illness, acoustic trauma, and genetic predisposition. Additionally, mammalian hair cells are susceptible to ototoxicity from a multitude of drugs including aminoglycoside antibiotics, loop diuretics, platinum-based chemotherapy agents, and a number of non-steroidal anti-inflammatory drugs (NSAIDS). Unfortunately unlike non-mammalian vertebrates, mammals are unable to regenerate damaged auditory mechanosensory cells which results in permanent hearing loss.

Regeneration of auditory hair cells is a promising approach to restore hearing. Previous studies show that targeting the transcription factor, Atoh1, in the adjacent supporting cells results in conversion to hair cell-like cells, but they do not reach full maturity. One focus of the Zuo lab is to target specific supporting cells that are more progenitor-like to achieve a higher rate, function, and maturity of conversion to hair cells. This project will utilize genetic mouse models together with various techniques such as drug delivery, immunofluorescence, confocal microscopy, scanning electron microscopy (SEM), RNA sequencing (RNAseq), and auditory brainstem response (ABR). A basic understanding of genetics would be helpful but is not required.

Project 2: Immunoresponses after cochlear damage

Over 20 million people over the age of 20 in the US have some hearing loss due to noise exposure at work or during activities such as sporting events or concerts. Excessive noise damages the delicate hair cells of the inner ear which cannot recover. The inner ear is a unique tissue that links the brain with a sensory epithelium that does not renew itself over our lifetime. At every other epithelial surface of the body, the immune system is present to prevent infection and damage. Recently, renewed interest in the immune system's involvement in the inner ear has followed discovery of a larger role of immune cells in the brain. It has been shown also that the cells of the immune system are resident in and infiltrate the inner ear following hearing damage. However, relatively little is known about these cells. My project aims to parse out the roles of these immune cells after noise damage.

The immune system has two arms that respond following infection or damage- the innate and the adaptive arms. The innate immune system infiltrates an area of damage or infection quickly causing inflammation. The adaptive immune system arrives later and is responsible for memory to pathogens, dampening inflammatory responses, and, in some cases, tissue regeneration. Using mouse models lacking the adaptive immune system, the student will examine which cell types and proteins of the adaptive immune system effect the inner ear epithelium following noise damage. This project will encompass numerous lab techniques including immunofluorescent confocal microscopy, flow cytometry, cell culture, bone marrow transplant, and RNAseq. Any discoveries from this project will have broad impacts in the field of immunology, hearing, epithelial biology, and tissue regeneration.